

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	Group Art Unit: 1637
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Lau et al.)	Examiner: Bertagna, Angela M.
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Serial No.: 10/780,963)	
)	
Filed: Feb. 18, 2004)	
)	
For: Polyelectrolyte-Coated Size-Exclusion)	
Ion-Exchange Particles)	
)	
Confirmation No.: 8953)	
)	
)	

Declaration of Aldrich N.K. Lau Under 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Aldrich N. K. Lau, declare and affirm as follows:

1. I am a Scientific Fellow in Research and Development for the Applied Biosystems Group of Applera Corporation in Foster City, California.
2. I hold a Ph.D. in synthetic organic chemistry, held a three year appointment as a Postdoctoral Fellow, and have 25 years experience in R&D in the private sector. I am the author or coauthor of over 20 peer reviewed papers, as well as a named inventor on 17 issued US patents, as well as 25 US published patent applications.
3. I am an inventor on the present patent application (ASN 10/780,963).

4. I am familiar with the field of materials science related to biological analysis and during my work at Applied Biosystems, I have become highly familiar with the field of the preparation of polynucleic acid-containing samples for analysis.

5. I have reviewed the above-identified patent application, the pending claims, and the Office action dated November 11, 2007. From reading the Office action, I understand that the previous claims were rejected by the Examiner for alleged obviousness. Particularly, the previous independent claims of the present application are rejected as allegedly obvious over a published application to Parthasarathy et al. (US 2003/0138779; hereafter Parthasarathy) in view of Ramstad et al (US 2003/0228706; hereafter Ramstad). For reasons as stated in the following, I disagree with the rejection.

6. The Examiner stated that Parthasarathy teaches a method for purifying PCR reaction products and DNA sequencing reaction products comprising providing a plurality of particles, where each particle comprises an ion exchange core coated by exposing the core to a polyelectrolyte polymer (Action; pg 3). The Examiner further states that Parthasarathy teaches the steps of providing a plurality of particles, and contacting polynucleotide-containing samples with a plurality of particles (Action; pg 3). In the Action, the Examiner stated that Parthasarathy teaches that the polyelectrolyte-coated ion exchange particles repel larger charged particles, while binding and retaining smaller contaminants, such as salts and unextended primers, citing paragraph 52 of Parthasarathy (Action, pg 5).

7. The Examiner has stated that Ramstad teaches a method for purifying PCR reaction products and DNA sequencing reaction products comprising providing a plurality of particles, wherein each particle, wherein each particle comprises a core for ion-exchange and a coating of polyelectrolyte (Action; pp 5-6). To support that statement, the Examiner refers to 20, and 53-56 of Ramstad. The Examiner has stated that one of ordinary skill in the art would recognize that the previously claimed methods of the present application are an obvious combination of the teachings of Parthasarathy and Ramstad (Action; pp 7-8).

8. It is my understanding that a person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. One of ordinary skill in the art of the preparation of biological samples for analysis would recognize that preparation of biological samples for analysis using solid phase extraction (SPE) may use the same or similar protocol for SPE regardless of the type of SPE material. For example, steps, such as providing the media, contacting the sample with the media, isolating the sample from the media, and performing an analysis may be performed by the very nature of the solid phase extraction process regardless of a great variety of SPE media. However, not all of the great variety of SPE media may provide the same results for any one particular sample prepared for a specific analysis. In fact, as one of ordinary skill in the art of sample preparation for biological analysis is apprised, SPE media may work on vastly different principles, and may be found, through extensive experimentation, to meet some objectives for the preparation of a sample for a particular analysis, but fail to meet other objectives.

9. With respect to Parthasarathy, one of ordinary skill in the art would gain nothing from the teachings of the steps of Parthasarathy, since, as previously mentioned, the steps for SPE using any of a variety of SPE media may be the same. One aspect of the difference between the coated anion exchange material provided in the methods of Parthasarathy and

the particles provided in the methods of the present application is the coating itself. Parthasarathy teaches the use of polyelectrolyte homopolymers and polyalkylene oxide polymers with charged end groups as coating materials. Additionally, Parthasarathy teaches that the coating is a partial coating. For example, in Example 2, Table 1, a polyelectrolyte homopolymer, poly(sodium 4-styrene-sulfonate), or PSSA, is used at fairly low challenge concentrations of between about 0.01 wt % to about 0.10 wt%. At the lowest concentrations of about 0.01 wt % to about 0.05 wt%, the interfering organic species are successfully removed, but so are significant amounts of the desired sequencing ladder species. At a loading of about 0.10 wt%, all of the desired sequencing ladder species remain in solution, but an appreciable concentration of interfering species is not removed. It appears to me from these data that both the analytical species of interest, as well as the interfering species compete for sites on the anion exchange media. From the data presented in Parthasarathy, it appears that the coating must be partial, as there must be enough polyelectrolyte coating of Parthasarathy to block sites that sequencing ladder species might occupy, and at the same time, not too much coating that would reduce sites for the organic species to bind. Unlike the particles provided in methods of the present application, this means that the polyelectrolyte homopolymer coating of Parthasarathy is not adapted to leave the desired species in solution.

10. The present application provides several figures and associated description of exemplary methods for sample preparation of dye-labeled polynucleotides, for PCR reaction products or DNA sequencing reaction products, for example. Attention is directed to FIG. 10 of the present application. In FIG. 10, the capillary electrophoresis results, or electropherograms, are shown that compare the sample preparation of a PCR reaction mixture as described for FIG. 8 for particles coated with different preparations of a coating material. For these experiments, synthetic copolymer materials prepared using a charged monomer, acrylic acid (AA), and a neutral co-monomer, dimethylacrylamide (DMA), were used for the coating of particles. The copolymers created using these two monomers is designated as poly(AA-co-DMA) (see also FIG. 2a). In the experiment represented in FIG. 10, the molar % of AA in the poly(AA-co-DMA) ranges from 1.1 molar % on the bottom, to 100% at the top. The results at the top represent a sample prepared using a particle coated with a polyelectrolyte homopolymer, while the sample at the bottom represents a copolymer with only 1.1% of charged species. From the data of FIG. 10, it is clear that if polyelectrolyte homopolymers or polymers having only charged end groups were used to coat the ion-exchange particles, as taught by Parthasarathy, the result would be a resounding failure to provide sample preparation of dye-labeled polynucleotides. Surprisingly, the data in FIG. 10 demonstrate that the polyelectrolyte copolymer coatings of the present application provide unpredictable results.

11. With respect to Ramstad, I am very familiar with Ramstad, as I am a co-inventor on that patent application, now an issued patent, US 6, 833, 238. As a synthetic organic chemist, I am highly familiar with the particles described in Ramstad. The statement by the Examiner asserting that the particles taught in Ramstad are an ion-exchange core coated by a polyelectrolyte is incorrect. First, I can find nothing in paragraph 20 of Ramstad that indicates that the particles taught in Ramstad are composed of an ion-exchange core coated by a polyelectrolyte. Second, paragraphs 53-56 teach how to make an ion-exchange material from a particle having a solid core, such as controlled pore glass. Finally, the particle is not a coated particle, but a particle around which a jacket or shell of a neutral

polymer is synthesized. There is no support in Ramstad for a particle as claimed in the present application.

12. In summary, for the reasons presented above, the present invention constitutes a true innovation in the field of methods for the preparation of polynucleic acid-containing samples. For methods based on solid phase extraction, the nature of the SPE media may be differentiating in providing a targeted result. This is especially true for highly complex samples, such as biological samples, which contain an array of chemical moieties having vastly different properties. The present application, in which methods utilizing a family of SPE particles are taught, and in which data is presented that demonstrates surprising and unpredictable results, warrants the grant of a patent.

13. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

March 7, 2008

Date



Aldrich N. K. Lau